PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Symdeko Prior Authorization Policy
- Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets – Vertex)

REVIEW DATE: 02/07/2024; selected revision 04/10/2024

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Symdeko is indicated for the treatment of **cystic fibrosis** (CF) in patients ≥ 6 years of age who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.[1]

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. Table 1 lists the responsive CFTR mutations based on: 1) a clinical forced expiratory volume in 1 second (FEV_1) response and/or 2) *in vitro* data in Fischer rat thyroid cells, indicating that tezacaftor/ivacaftor increases chloride transport to ≥ 10% of untreated normal over baseline. CFTR gene mutations that are not responsive to Kalydeco® (ivacaftor granule or tablet) alone are not expected to respond to Symdeko except for F508del homozygotes.

Table 1. List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko.[1]

E56K	*E193K*	*S945L*	*F1074L*
P67L	*L206W*	*S977F*	*D1152H*

R74W	*R347H*	*F1052V*	*D1270N*
D110E	*R352Q*	*E831X*	*2789+5G→A*
D110H	*A455E*	*K1060T*	*3272-26A→G*
R117C	*D579G*	*A1067T*	*3849 + 10kbC→ T*
F508del[*]	*711+3A→G*	*R1070W*	*G622D*
A120T	*E60K*	*F1016S*	*G970D*
A234D	*E92K*	*F1099L*	*G1069R*
A349V	*E116K*	*G126D*	*G1244E*
A554E	*E403D*	*G178E*	*G1249R*
A1006E	*E558V*	*G178R*	*G1349D*
D192G	*E822K*	*G194R*	*H939R*
D443Y	*F191V*	*G194V*	*H1054D*
D443Y;G57A; R668C	*F311del*	*G314E*	*H1375P*
D614G	*F311L*	*G551D*	*I148T*
D836Y	*F508C*	*G551S*	*I175V*
D924N	*F508C;S1251N*	*G576A*	*I336K*
D979V	*F575Y*	*G576A;R668C*	*I601F*
I618T	*L346P*	*M952T*	*R74Q*
I807M	*L967S*	*P5L*	*R74W;D1270N*
I980K	*L997F*	*P205S*	*R74W;V201M*
I1027T	*L1324P*	*Q98R*	*R74W;V201M;D1270N*
I1139V	*L1335P*	*Q237E*	*R75Q*
I1269N	*L1480P*	*Q237H*	*R117G*
I1366N	*M152V*	*Q359R*	*R117H*
L15P	*M265R*	*Q1291R*	*R117L*
L320V	*M9521*	*R31L*	*R117P*
R170H	*R1066H*	*S1251N*	*W1282R*

Table 1 (continued). List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko.[1]

R258G	*R1070Q*	*S1255P*	*Y109N*
R334L	*R1162L*	*T338I*	*Y161S*
R334Q	*R1283M*	*T1036N*	*Y1014C*
R347L	*R1283S*	*T1053I*	*Y1032C*
R347P	*S549N*	*V201M*	*R792G*
R352W	*S549R*	*V232D*	*R933G*
R553Q	*S589N*	*V562I*	*S1159F*
R668C	*S737F*	*V754M*	*S1159P*
R751L	*S912L*	*V1153E*	*V1240G*
V1293G	*546insCTA*		

CFTR – Cystic fibrosis transmembrane regulator; [*] A patient must have two copies of the F508del mutation or at least one copy of a responsive mutation presented in Table 1 to be indicated.

Guidelines

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF; Symdeko is not addressed.[2]

According to the CF Foundation (2017), CF is diagnosed when an individual has both a clinical presentation of CF and evidence of CFTR dysfunction.[4,5] Clinical presentation of CF includes a positive newborn screening, signs and/or symptoms of CF, and/or family history of CF. To establish a diagnosis of CF, sweat chloride tests should be considered first, then CFTR genetic analysis (CFTR genotype), and then CFTR physiologic tests (nasal potential difference [NPD] or intestinal current measurement

[ICM]). However, tests of CFTR function are not always done in this order. All individuals diagnosed with CF should have a sweat chloride test and CFTR genetic analysis performed.

In a patient with a sweat chloride test ≥ 60 mmol/L, CF diagnosis is established and in patients with a sweat chloride test < 30 mmol/L, a diagnosis of CF is unlikely.[4,5] Rarely, patients with a sweat chloride < 30 mmol/L may be considered to have CF if alternatives are excluded and other confirmatory tests (genetic and physiologic testing) support CF. In patients with a sweat chloride test of ≥ 30 to < 60 mmol/L, CFTR genetic analysis is undertaken. If the genetic analysis identifies two CF-causing CFTR mutations, CF is diagnosed, if no CFTR mutations are identified, a diagnosis of CF is unlikely. In patients with a CFTR genotype that is undefined or of varying clinical consequence, full gene CFTR sequencing (if not already performed) or CFTR physiologic testing is performed (NPD or ICM). If only one CFTR variant is identified on limited analysis, full gene CFTR sequencing be performed. CF is possible if both alleles posses CF-causing, undefined, or mutation of varying clinical consequence mutations; CF is unlikely if only no CF-causing mutations are found. If results of the NPD or ICM show CFTR dysfunction, CF is diagnosed; when testing is unavailable or equivocal, the diagnosis of CF is not resolved, and when results of the physiologic testing show CFTR function is preserved, a diagnosis of CF is considered unlikely. It is recommended that patients with challenging diagnoses be evaluated at an accredited CF Foundation Care Center.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Symdeko. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Symdeko as well as the monitoring required for adverse events and efficacy, approval requires Symdeko to be prescribed by or in consultation with a physician who specializes in the condition being treated.

- **Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets (Vertex)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indication

1. **Cystic Fibrosis.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D and E):
   A) Patient is ≥ 6 years of age; AND
   B) Patient meets ONE of the following (i or ii):
      i. Patient has at least ONE of the following mutations in the cystic fibrosis transmembrane conductance regulator gene that is considered to be a pathogenic or likely pathogenic variant: E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3A →

G, S945L, S977F, F1052V, E831X, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5G → A, 3272-26A → G, 3849 + 10kbC → T, 546insCTA, A120T, A234D, A349V, A554E, A1006E, D192G, D443Y, D443Y;G57A;R668C, D614G, D836Y, D924N, D979V, I618T, I807M, I980K, I1027T, I1139V, I1269N, I1366N, L15P, L320V, R170H, R258G, R334L, R334Q, R347L, R347P, R352W, R553Q, R668C, R751L, V1293G, E60K, E92K, E116K, E403D, E558V, E822K, F191V, F311del, F311L, F508C, F508C;S1251N, F575Y, L346P, L967S, L997F, L1324P, L1335P, L1480P, M152V, M265R, M9521, R1066H, R1070Q, R1162L, R1283M, R1283S, S549N, S549R, S589N, S737F, S912L, F1016S, F1099L, G126D, G178E, G178R, G194R, G194V, G314E, G551D, G551S, G576A, G576A;R668C, M952T, P5L, P205S, Q98R, Q237E, Q237H, Q359R, Q1291R, R31L, S1251N, S1255P, T338I, T1036N, T1053I, V201M, V232D, V562I, V754M, V1153E, G622D, G970D, G1069R, G1244E, G1249R, G1349D, H939R, H1054D, H1375P, I148T, I175V, I336K, I601F, R74Q, R74W;D1270N, R74W;V201M, R74W;V201M;D1270N, R75Q, R117G, R117H, R117L, R117P, W1282R, Y109N, Y161S, Y1014C, Y1032C, R792G, R933G, S1159F, S1159P, or V1240G; OR

ii. Patient has TWO copies of the F508del mutation; AND

C) Patient meets at least ONE of the following (i, ii, or iii):

i. Positive cystic fibrosis newborn screening test; OR

ii. Family history of cystic fibrosis; OR

iii. Clinical presentation consistent with signs and symptoms of cystic fibrosis; AND

Note: Examples of clinical presentation of cystic fibrosis include but are not limited to meconium ileus, sino-pulmonary symptoms (e.g., persistent cough, wheezing, pulmonary function tests consistent with obstructive airway disease, excess sputum production), bronchiectasis, sinusitis, failure to thrive, pancreatic insufficiency.

D) Patient has evidence of abnormal cystic fibrosis transmembrane conductance regulator function as demonstrated by at least ONE of the following (i, ii, or iii):

i. Elevated sweat chloride test; OR

ii. Two cystic fibrosis-causing cystic fibrosis transmembrane conductance regulator mutations; OR

iii. Abnormal nasal potential difference; AND

E) The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

CONDITIONS NOT COVERED

- **Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets (Vertex)**

is(are) considered experimental, investigational or unproven for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Cystic Fibrosis (CF), Patient with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation.** An FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of Symdeko.[1]

2. **Combination Therapy with Orkambi, Kalydeco, or Trikafta.** Symdeko contains ivacaftor, the active agent in Kalydeco and part of Orkambi and Trikafta. Symdeko also contains tezacaftor, part of Trikafta. Symdeko is not indicated in combination with Kalydeco, Orkambi, or Trikafta.

3. **Infertility.** Symdeko is indicated for the treatment of cystic fibrosis in a patient ≥ 6 years of age who is homozygous for the F508del mutation or who has at least one mutation in the cystic fibrosis transmembrane conductance regulator gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.[1] Note: A patient with a diagnosis of cystic fibrosis should be reviewed using criteria for the FDA-approved indication, above.

REFERENCES

1. Symdeko® tablets [prescribing information]. Cambridge, MA: Vertex; August 2023.
2. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271-280.
3. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr*. 2017;181S:S4-S15.
4. Farrell PM, White TB, Howenstine MS, et al. Diagnosis of cystic fibrosis in screened populations. *J Pediatr.* 2017;181S:S33-S44.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	02/08/2023
Annual Revision	No criteria changes.	02/07/2024
Selected Revision	**Cystic Fibrosis (CF):** The criterion that the patient has at least one of the following mutations in the cystic fibrosis transmembrane conductance regulator gene, was modified to require that the mutation be considered pathogenic or likely pathogenic. A criterion was added to require the patient has at least one of the following: positive cystic fibrosis newborn screening test, family history of cystic fibrosis, or a clinical presentation consistent with signs and symptoms of cystic fibrosis. A criterion was added to require that the patient has evidence of abnormal cystic fibrosis transmembrane conductance regulator function as demonstrated by at least one of the following: elevated sweat chloride test, two cystic fibrosis-causing cystic fibrosis transmembrane conductance regulator mutations, or an abnormal nasal potential difference. **Infertility:** This indication was added to Conditions Not Covered	04/10/2024